



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: C07D 233/54, 233/84, 401/04, A61K 31/415, 31/44	A1	(11) International Publication Number: WO 99/03837 (43) International Publication Date: 28 January 1999 (28.01.99)
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(54) Title: 2-SUBSTITUTED IMIDAZOLES USEFUL IN THE TREATMENT OF INFLAMMATORY DISEASES (57) Abstract <p>This invention relates to substituted imidazoles of Formula (I), pharmaceutical compositions containing them, methods of using them and intermediates useful in their manufacture. The compounds of the invention modulate the production of a number of inflammatory cytokines, and are useful in the treatment of diseases associated with the production of inflammatory cytokines.</p> <div data-bbox="954 1129 1295 1276"><p>(I)</p></div>		

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2-SUBSTITUTED IMIDAZOLES USEFUL IN THE TREATMENT OF INFLAMMATORY DISEASES

This invention relates to a series of substituted imidazoles, pharmaceutical compositions containing them and intermediates used in their manufacture. The compounds of the invention inhibit the production of a number of inflammatory cytokines, particularly, TNF- α , and IL-1 β . Compounds of this invention are useful in the treatment of diseases associated with overproduction of inflammatory cytokines, such as rheumatoid arthritis, inflammatory bowel disease, septic shock, osteoporosis, and osteoarthritis.

BACKGROUND OF THE INVENTION

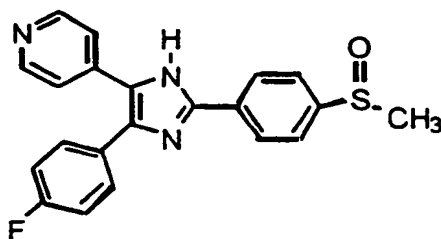
The inflammatory cytokines, IL-1 β and TNF- α play an important role in a number of inflammatory diseases such as rheumatoid arthritis. C. Dinarello et al., Inflammatory cytokines: Interleukin-1 and Tumor Necrosis Factor as Effector Molecules in Autoimmune Diseases *Curr. Opin. Immunol.* **1991**, 3, 941-48. Arthritis is an inflammatory disease which affects millions of people and can strike at any joint of the human body. Its symptoms range from mild pain and inflammation in affected joints, to severe and debilitating pain and inflammation. Although the disease is associated mainly with aging adults, it is not restricted to adults. The most common arthritis therapy involves the use of nonsteroidal antiinflammatory drugs (NSAID) to alleviate the symptoms. However, despite their widespread use, many individuals cannot tolerate the doses necessary to treat the disease over a prolonged period of time. In addition, NSAIDs merely treat the symptoms of disease without affecting the underlying cause. Other drugs, such as methotrexate, gold salts, D-pencillamine, and prednisone are often used when patients fail to respond to NSAIDS. These drugs also have significant toxicities and their mechanism of action remain unknown.

Receptor antagonists to IL-1 β and monoclonal antibodies to TNF- α have been shown to reduce symptoms of rheumatoid arthritis in small-scale human clinical trials. In addition to protein based therapies, there are small molecule agents which inhibit the production of these cytokines and have demonstrated activity in animal arthritis models. J.C. Boehm et al., 1-Substituted 4-Aryl-5-pyridinylimidazoles: A New Class of Cytokine

Suppressive Drugs With Low 5-Lipoxygenase and Cyclooxygenase Inhibitory Potency, *J. Med. Chem.*, 1996, 39, 3929-37. Of these small molecule agents, SB 203580 has proved effective in reducing the production of TNF- α and IL-1 in LPS stimulated human monocyte cell lines with IC₅₀ values of 50 to 100 nM.

- 5 J. Adams et al., Imidazole Derivatives And Their Use as Cytokine Inhibitor, International Patent application WO 93/14081, July 23, 1993. In addition to this in vitro test, SB 203580 inhibits the production of the inflammatory cytokines in rats and mice at IC₅₀ values of 15 to 25 mg/kg. A.M. Badger, et al, Pharmacological Profile of SB 203580, A Selective Inhibitor of Cytokine
- 10 Suppressive Binding Protein/p38 Kinase, in Animal Models of Arthritis, Bone Resorption, Endotoxin Shock and Immune Function, *The Journal of Pharmacology and Experimental Therapeutics*, 1996, 279, 1453-61. Although human data is currently unavailable for SB 203580, monoclonal antibodies to TNF- α have proved efficacious in the treatment of rheumatoid arthritis. M.J.
- 15 Elliot et al., Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α , *Arthritis Rheum.* 1993 36, 1681-90. Due to SB 203580's oral activity and potency in animal models, researchers have suggested that a compound with this profile has potential as a viable treatment for rheumatoid arthritis. A.M. Badger, et al. Pharmacological Profile
- 20 of SB 203580, A Selective Inhibitor of Cytokine Suppressive Binding Protein/p38 Kinase, in Animal Models of Arthritis, Bone Resorption, Endotoxin Shock and Immune Function, *The Journal of Pharmacology and Experimental Therapeutics*, 1996, 279, 1453-61.

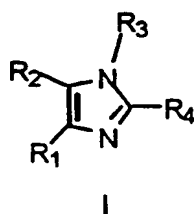
- SB 203580 and other small molecule agents reduce the production of
- 25 inflammatory cytokines by inhibiting the activity of a serine/threonine kinase p38 (note other researchers refer to this enzyme as CSBP), at an IC₅₀ of 200 nM. D. Griswold et al., Pharmacology of Cytokine Suppressive Anti-inflammatory Drug Binding Protein (CSPB), A Novel Stress-Induced Kinase, *Pharmacology Communications*, 1996, 7, 323-29. Although the precise mechanism of this
- 30 kinase is unknown, it has been implicated in both the production of TNF- α and the signaling responses associated with the TNF- α receptor.



SB 203580

SUMMARY OF THE INVENTION

The invention relates to compounds of the Formula I



wherein:

R₁ is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or substituted phenyl

wherein the substituents are independently selected from one or members of the group consisting of C₁₋₅alkyl, halogen, nitro, trifluoromethyl and nitrile;

R₂ is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, substituted heteroaryl

wherein the substituents are independently selected from one or more members of the group consisting of C₁₋₅alkyl and halogen, or

substituted phenyl

wherein the substituents are independently selected from one or members of the group consisting of C₁₋₅alkyl, halogen, nitro, trifluoromethyl and nitrile;

R_3 is hydrogen, SEM, C_{1-5} alkoxycarbonyl, aryloxycarbonyl, aryl C_{1-5} alkyloxycarbonyl, aryl C_{1-5} alkyl, phthalimido C_{1-5} alkyl, amino C_{1-5} alkyl, diamino C_{1-5} alkyl, succinimido C_{1-5} alkyl, C_{1-5} alkylcarbonyl, arylcarbonyl, C_{1-5} alkylcarbonyl C_{1-5} alkyl, aryloxycarbonyl C_{1-5} alkyl, heteroaryl C_{1-5} alkyl where the heteroaryl contains 5 to 6 ring atoms, or substituted aryl C_{1-5} alkyl

wherein the aryl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, C_{1-5} alkoxy, halogen, amino, C_{1-5} alkylamino, and di C_{1-5} alkylamino;

R_4 is $(A)_n-(CH_2)_q-X$ wherein:

A is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X is selected from the group consisting of hydrogen, hydroxy, halogen, vinyl, ethynyl, C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{1-5} alkoxy, phenoxy, phenyl, aryl C_{1-5} alkyl, amino, C_{1-5} alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, C_{1-5} alkylthio, C_{1-5} alkylsulfonyl, phenylsulfonyl, substituted sulfonamido

wherein the sulfonyl, substituent is selected from the group consisting of C_{1-5} alkyl, phenyl, aryl C_{1-5} alkyl, thienyl, furanyl, and naphthyl;

substituted vinyl

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine ,

substituted ethynyl

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted C₁₋₅alkyl

5

wherein the substituents are selected from the group consisting of one or more C₁₋₅alkoxy, trihaloalkyl, phthalimido and amino,

substituted phenyl

10

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy,

substituted phenoxy

15

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy,

substituted C₁₋₅alkoxy

wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,

substituted arylC₁₋₅alkyl

20

wherein the alkyl substituent is hydroxyl,

substituted arylC₁₋₅alkyl

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy,

25

substituted amido

wherein the carbonyl substituent is selected from the group consisting of C₁₋₅alkyl, phenyl, arylC₁₋₅alkyl, thienyl, furanyl, and naphthyl,

substituted phenylcarbonyl

30

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy,

substituted C₁₋₅alkylthio

wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido, substituted C₁₋₅alkylsulfonyl

5 wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido, substituted phenylsulfonyl

wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C₁₋₅alkoxy and
10 trifluoromethyl,

with the proviso:

if A is sulfur and X is other than hydrogen, C₁₋₅alkylaminocarbonyl, phenylaminocarbonyl, arylC₁₋₅alkylaminocarbonyl, C₁₋₅alkylsulfonyl or phenylsulfonyl, then q must be equal to or
15 greater than 1;

if A is sulfur and q is 1, then X cannot be C₁₋₂alkyl;

if A is carbonyl and q is 0, then X cannot be vinyl, ethynyl, C₁₋₅alkylaminocarbonyl, phenylaminocarbonyl,

arylC₁₋₅alkylaminocarbonyl, C₁₋₅alkylsulfonyl or phenylsulfonyl;

20 if A is carbonyl, q is 0 and X is H, then R₃ is not SEM;

if n is 0 and q is 0, then X cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

In addition this invention contemplates pharmaceutical compositions containing compounds of Formula I, and methods of treating cytokine
25 mediated disorders with compounds of Formula I.

The novel compounds of this invention inhibit the in vitro activity of p-38 in the nanomolar range. In addition, the compounds inhibit the in vitro secretion of TNF- α and IL-1 β in the nanomolar range. Animal models demonstrate the inhibition of LPS induced TNF- α , as well as the inhibition of
30 rheumatoid arthritis. With this range of activity the compounds of the invention are useful in the treatment of a variety of cytokine related disorders including: rheumatoid arthritis, inflammatory bowel disease, septic shock osteoporosis,

osteoarthritis, neuropathic pain, HIV replication, HIV dementia, viral myocarditis, insulin-dependent diabetes, non-insulin dependent diabetes, periodontal disease, restenosis, alopecia areta, T-cell depletion in HIV infection or AIDS, psoriasis, acute pancreatitis, allograft rejection, allergic inflammation in the lung, atherosclerosis, multiple sclerosis, cachexia, 5 alzheimer's disease, stroke, Crohn's disease, inflammatory bowel disease, ischemia, congestive heart failure, pulmonary fibrosis, hepatitis, glioblastoma, Guillain-Barre Syndrome, and systemic lupus erythematosus.

DETAILED DESCRIPTION OF THE INVENTION

10 The terms used in describing the invention are commonly used and known to those skilled in the art. However, the terms that could have other meanings are defined. The term "FCS" represents fetal calf serum, "TCA" represents trichloroacetic acid and the "RPMI" represents the medium from the Roswell Park Memoria Inst. (Sigma cat # R0833). "Independently" means that when there are 15 more than one substituent, the substituents may be different. The term "alkyl" refers to straight, cyclic and branched-chain alkyl groups and "alkoxy" refers to O-alkyl where alkyl is as defined supra. The term heteroaryl refers to an aromatic ring of five or six members where at least one member is a heteroatom. Suitable heteroatoms include, nitrogen, oxygen and sulfur. In the case of five-membered 20 rings the heteroaryl will contain one sulfur, oxygen, or nitrogen atom and, in addition, may contain up to three additional nitrogens. With six-membered rings the heteroaryl may contain up to three nitrogens. Examples of such heteroaryls include, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-3-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyridazine, triazine, thiazole, oxazole, pyrazole and 25 the like. "SEM" refers to 2-(trimethylsilyl)ethoxymethyl and "LDA" refers to lithium diisopropylamide. The symbol "Ph" refers to phenyl, "PHT" refers to phthalimido and the "aryl" includes mono and fused aromatic rings such as phenyl and naphthyl.

As used in this invention the term "cytokine" refers to the proteins TNF- α 30 and IL-1 β . Cytokine related disorders are diseases of humans and other mammals where the overproduction of cytokines causes the symptoms of the disease. The overproduction of the cytokines, TNF- α and IL-1 β has been linked to a number of diseases. These cytokine related disorders include but are not limited to rheumatoid arthritis, inflammatory bowel disease, septic shock 35 osteoporosis, osteoarthritis, neuropathic pain, HIV replication, HIV dementia, viral myocarditis, insulin-dependent diabetes, non-insulin dependent diabetes,

periodontal disease, restenosis, alopecia areata, T-cell depletion in HIV infection or AIDS, psoriasis, acute pancreatitis, allograft rejection, allergic inflammation in the lung, atherosclerosis, multiple sclerosis, cachexia, Alzheimer's disease, stroke, Crohn's disease, inflammatory bowel disease, ischemia, congestive heart failure, pulmonary fibrosis, hepatitis, glioblastoma, Guillain-Barre Syndrome, and systemic lupus erythematosus. The term "effective dose" refers to an amount of a compound of Formula I which reduces the amount of $\text{TNF}\alpha$ and/or $\text{IL-1}\beta$ which may be detected in a mammal suffering from a cytokine mediated disorder. In addition, the term "effective dose" refers to an amount of a compound of Formula I which reduces the symptoms of a cytokine related disorder.

The compounds of the invention may be prepared by the following schemes, where some schemes produce more than one embodiment of the invention. In those cases, the choice scheme is a matter of discretion that is well within the capabilities of those skilled in the art.

Scheme I may be used to produce the compounds of the invention where A is sulfur. The starting material for this scheme is a mercapto imidazole as exemplified by intermediate 1a. This intermediate may be prepared following known imidazole preparations. Lantos, I. et al. *J. Org. Chem.*, 1988, 53, 4223-27; Markova, Y. et al. *Zh. Org. Zhim.* 1965, 1, 1475. Intermediate 1a is treated with a base such as NaH, or *n*-BuLi in an inert solvent such as DMF or THF at room temperature over 30 minutes to several hours. This reaction mixture is treated with an alkylating agent such as 1-bromopentane to give the desired compound 1b. This reaction sequence may be used to produce the compounds of the invention where A is sulfur, n is 1, q is 0-9 and X is hydrogen, vinyl, ethynyl, substituted ethynyl, C_{1-5} alkyl, C_{3-7} cycloalkyl, substituted C_{1-5} alkyl, C_{1-5} alkoxy, aryl C_{1-5} alkyl, substituted aryl C_{1-5} alkyl, nitrile or C_{1-5} alkylamino, by modifying the alkylating agent with known compounds. For example to produce a compound of the invention where A is sulfur, n is 1 q is 0 and X is aryl C_{1-5} alkyl, one may treat intermediate 1a with benzyl chloride.

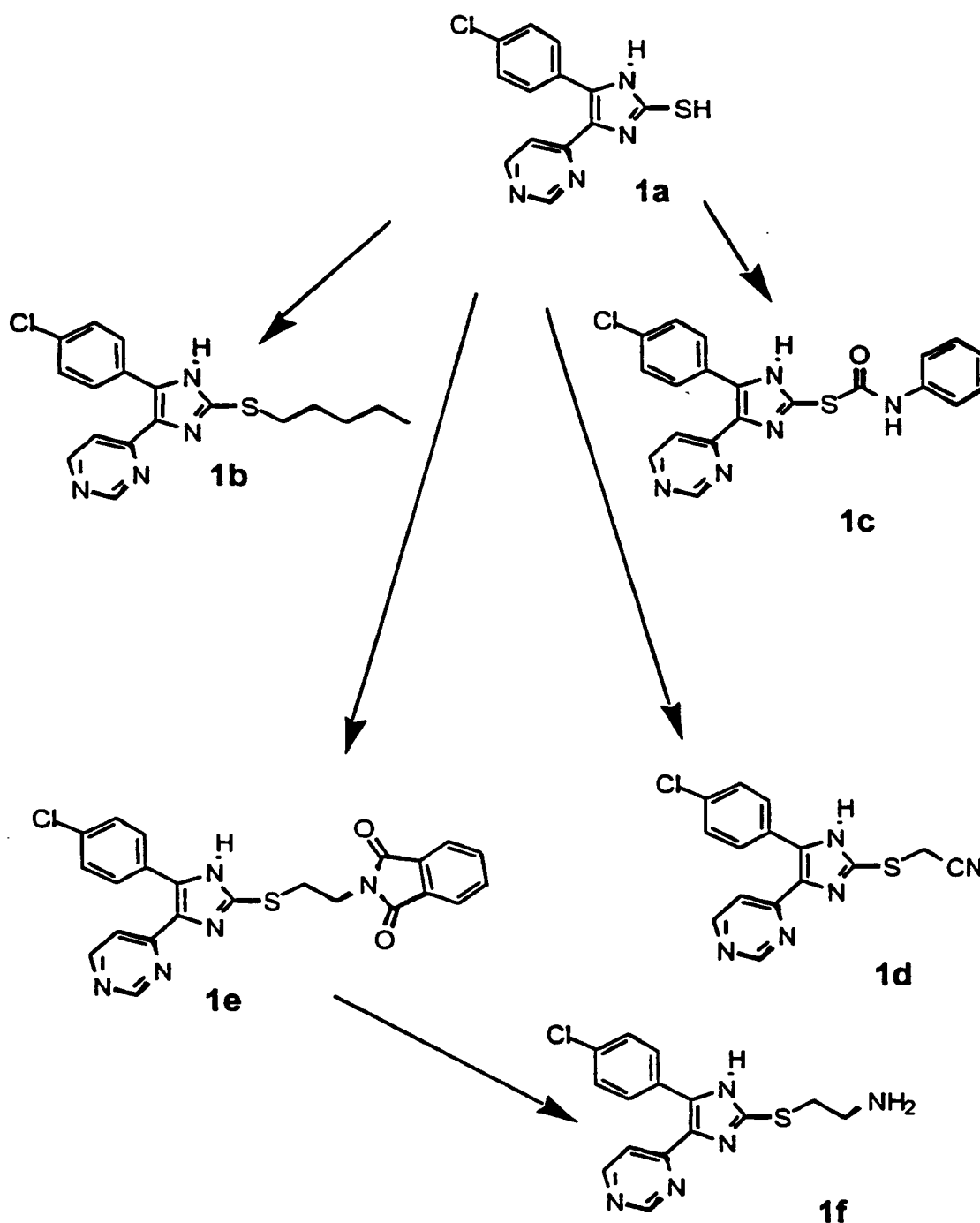
To produce the compounds of the invention where A is sulfur, n is 1, q is 0 and X is phenylaminocarbonyl, intermediate 1a is treated with a base such as NaH, or *n*-BuLi in an inert solvent such as DMF or THF at room temperature over 30 minutes to several hours. This reaction mixture is treated with an isocyanate, such as phenylisocyanate at room temperature over 1 to 24 hours. This reaction sequence may be used to produce the compounds 1c of the invention where A is sulfur, n is 1, q is 0 and X is C_{1-5} alkylaminocarbonyl by using known isocyanates. In addition, this sequence may be used to produce compounds where X is phenylcarbonyl, substituted phenylcarbonyl and C_{1-5} alkylcarbonyl. Replacement

of the isocyanate with a known substituted acyl halide derivative, such as 2-bromoacetophenone, gives the compound of the invention where X is phenylcarbonyl.

The compounds of the invention where A is sulfur, n is 1, q is 1 and X is nitrile may be produced as illustrated in Scheme I. Intermediate 1a is treated with a base such as NaH, or *n*-BuLi in an inert solvent such as DMF or THF at room temperature over 30 minutes to several hours. This reaction mixture is treated with an acetonitrile derivative such as iodoacetonitrile over several hours at room temperature to give compounds of the type 1d. In addition to compounds of the type 1d, one may use this sequence to produce compounds where A is sulfur, n is 1, q is 1 or greater and X is vinyl or ethynyl. These compounds may be prepared by replacing iodoacetonitrile with allyl halides or propargyl halides respectively.

Scheme I may be used to produce compounds of the invention where A is sulfur, n is 1, q is greater than 1 and X is phthalimido. Intermediate 1a is treated with a bases such as NaH, or *n*-BuLi in an inert solvent such as DMF or THF at room temperature over 30 minutes to several hours. This reaction mixture is treated with an haloalkylphthalimido derivative for 1 to several hours to give compounds of type 1e. To produce compounds where X is amino, compounds of type 1e are treated with hydrazine to give compounds of type 1f.

SCHEME 1

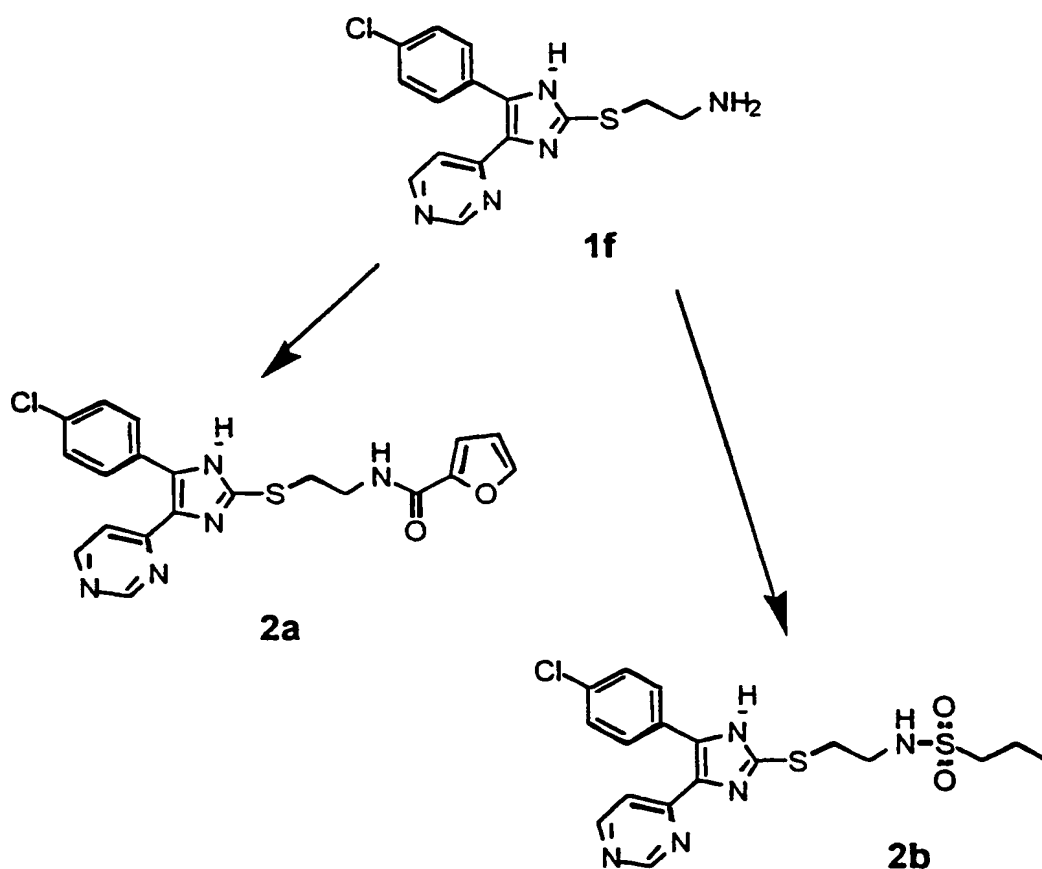


Other compounds of the invention may be produced via Scheme 2 using compounds of type 1f as starting materials. Compound 1f and furoyl chloride are treated with a mild base such as sodium bicarbonate and an inert solvent, such as DMF, at room temperature for 1 to several hours to give compounds of type 2a.

The compounds of the invention where X is carbonyl substituted amido, may be prepared via this method. For example, to prepare a compound where where A is sulfur, n is 1, q is 2 and X is naphth-2-ylamido, 2-naphthoyl chloride may be used in place of furoyl chloride to give the desired compound.

- 5 In addition, this scheme may be used to prepare compounds where X is substituted sulfonamido of the type 2b. Replacement of furoyl chloride by propanesulfonyl chloride gives compounds of type 2b.

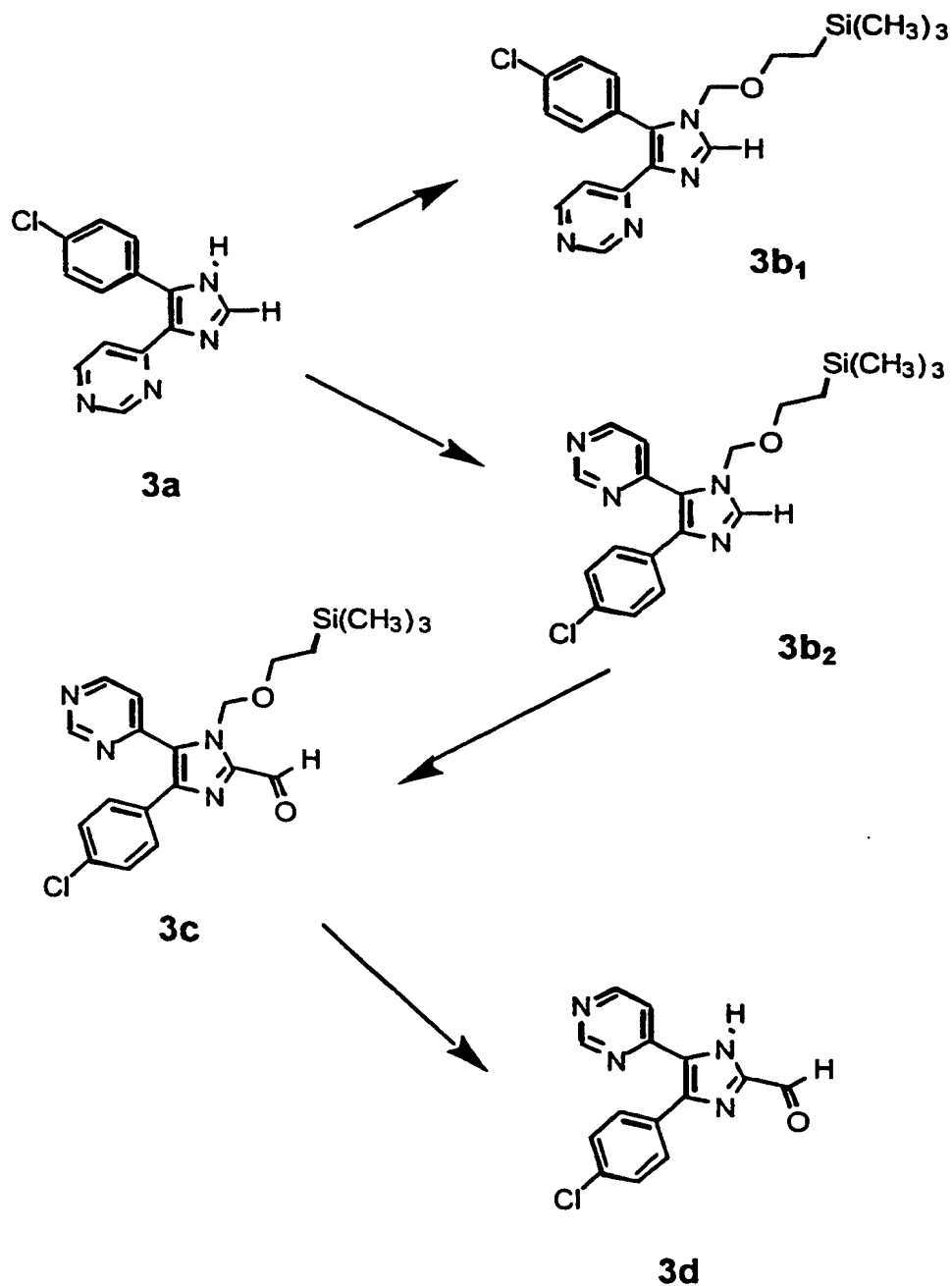
SCHEME 2



- 10 To produce the compounds of the invention where A is carbonyl, n is 1, q is 0 and X is hydrogen, Scheme 3 may be used. The starting imidazole, 3a, may be prepared following literature preparations (See eg., Klaus Hofmann, Imidazole and Its Derivatives Part I (1953)). This material is treated with bases such as NaH, or *n*-BuLi in an inert solvent such as DMF or THF at room temperature over
- 15 15 minutes to several hours. This reaction mixture is treated with a nitrogen

protecting group which is stable to basic conditions, such as 2,2-(trimethylsilyl)ethoxymethyl chloride at room temperature over 1 to 24 hours to give the 1-substituted imidazoles 3b₁ and 3b₂. The isomers 3b₁ and 3b₂ may be independently treated with a base, such as *n*-BuLi, and an inert solvent, such as THF, at about -78 °C under an inert atmosphere for about 15-30 min. This mixture is treated with a formylating agent, such as DMF, at room temperature for about 1 h to give compounds of type 3c. Treatment of intermediate 3c with an aqueous acid such as 1N HCl at room temperature for about 30 min to several hours gives 3d. This reaction sequence may be used to produce the compounds of the invention where A is carbonyl, q is 0-9, and X is C₁₋₅alkyl, phenyl and arylC₁₋₅alkyl by replacing the formylating agent with an acylating agent. For example to prepare a compound where A is carbonyl, q is 1, and X is phenyl, replace the formylating agent with benzoyl chloride. In addition compounds where A is carbonyl, q is 0-9 and X is hydroxy can be prepared by replacing the alkylating agent with cyclic lactones. For example, to prepare a compound where A is carbonyl, q is 3 and X is hydroxy, intermediate 3a is treated with butyrolactone.

SCHEME 3

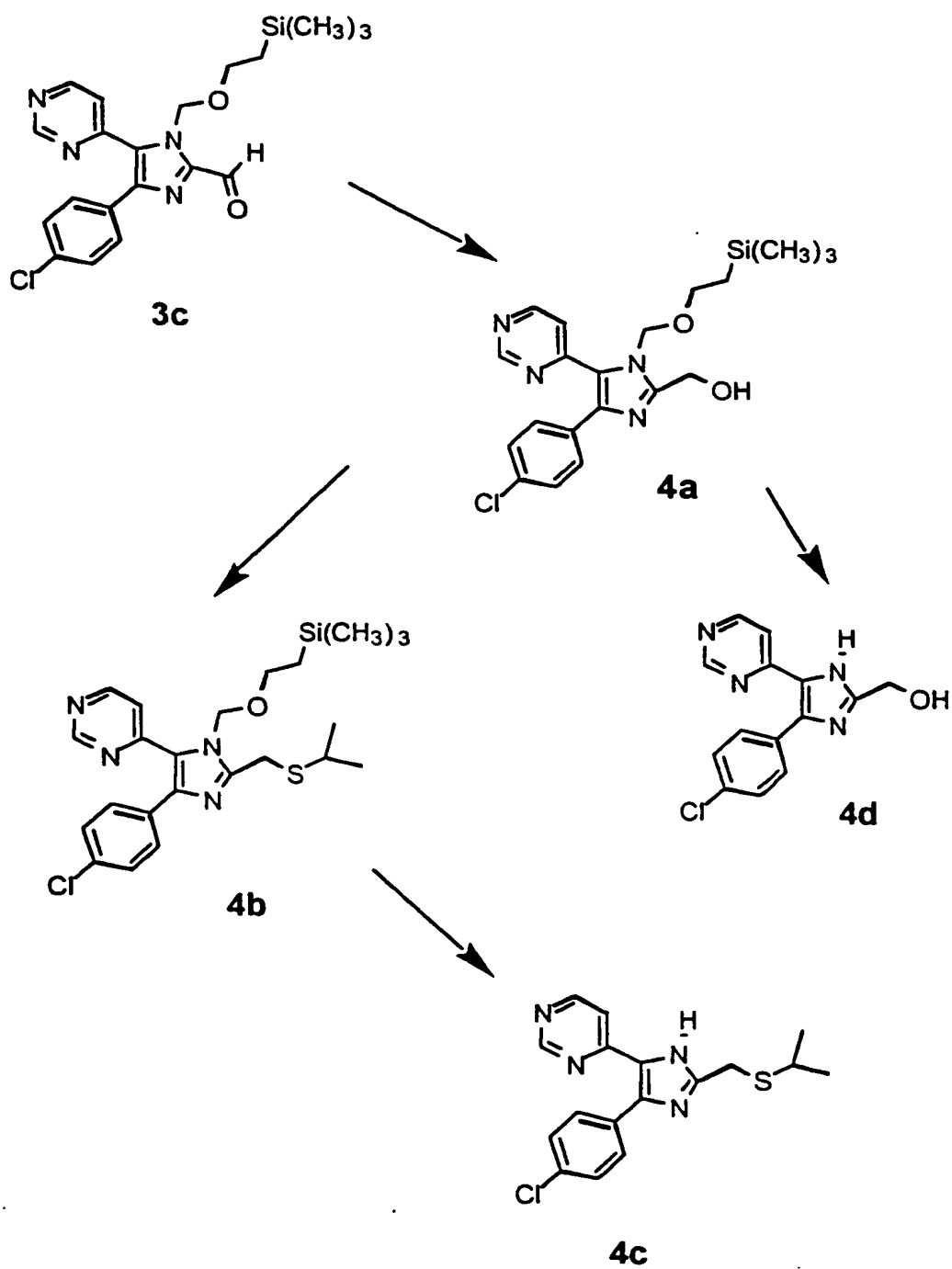


To prepare compounds of the invention where n is 0, intermediates from Scheme 3, may be used in Scheme 4. Intermediate 3c may be treated with H₂

and a hydrogenation catalyst such as Pd/C, at room temperature over 1 to several hours to give the alcohol 4a. This alcohol may be activated with triphenylphosphine or carbon tetrachloride and displaced with a nucleophilic agent such as 2-propanethiol at room temperature for 15 to 48 hours to give compounds of formula 4b. Treatment of 4b with aqueous acids such as 1N HCl at room temperature over several hours gives compounds of type 4c. This scheme may be used to produce compounds where X is substituted amino by modifying the nucleophilic agent. For example if one replaces 2-propanethiol with propylamine, a compound where n is 0, q is 1 and X is propylamino may be prepared.

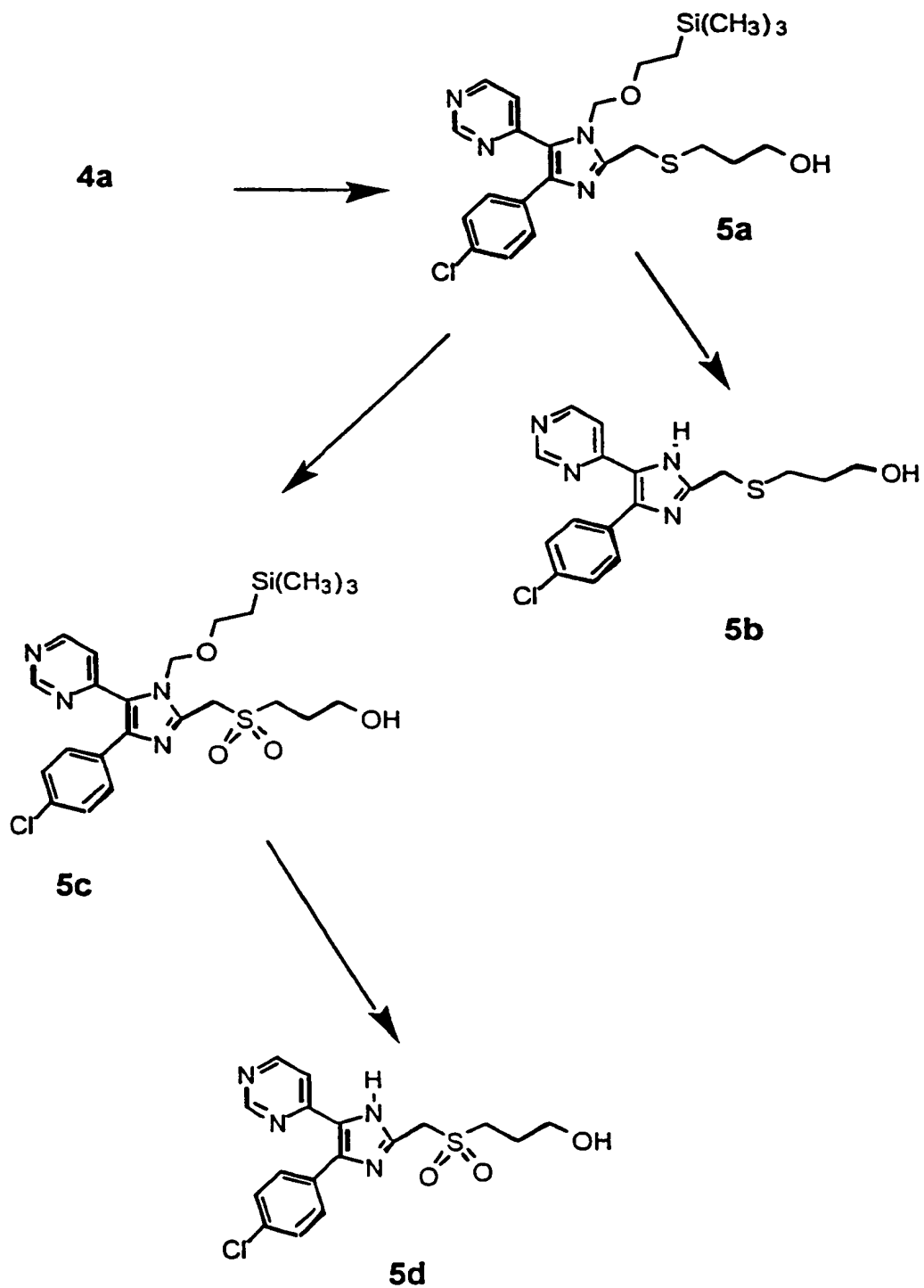
Aside from nucleophilic displacement, alcohol 4a may be may be treated with aqueous acids such as 1N HCl at room temperature over several hours to give the unprotected alcohol 4d. This unprotected alcohol may be used to prepare other compounds of the invention. For example, to prepare a compound where n is 0, q is 1 and X is C₁₋₅alkoxy, compound 4d is treated with a base such as NaH and an alkylating agent such as propyl bromide at room temperature.

SCHEME 4



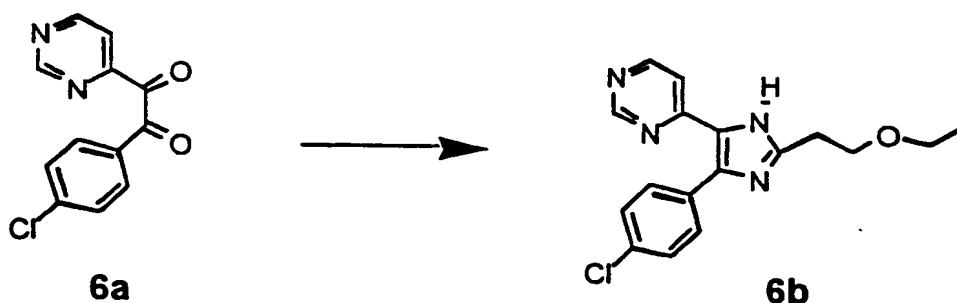
- To prepare compounds where n is 0 and X is C₁₋₅alkylsulfonyl or alkyl substituted C₁₋₅alkylsulfonyl, Scheme 5 may be used. Intermediate 4a is treated with a hydroxyl activating group, such as triphenylphosphine and carbon tetrachloride in an inert solvent, such as acetonitrile. The activated intermediate is
- 5 treated with an alkylating group such as 2-mercaptoethanol and an organic or inorganic base such as NaOH at about room temperature to reflux for several hours to give intermediates of the type 5a. As discussed previously, intermediate 5a may be treated with acidic solutions to give imidazol-2-yl substituted compounds of type 5b. Alternatively, intermediate 5a may be treated with
- 10 oxidizing agents such as oxone in an inert solvent such as MeOH at ambient temperature over about 4-14 hours to give sulfones of type 5c. Finally intermediates such as 5c may be treated with aqueous acid solutions to give imidazol-2-yl substituted compounds of type 5d.

SCHEME 5



Although the preceding schemes start with an unsubstituted imidazole ring, many of the compounds of the invention may be prepared by forming the imidazole with the desired 2-substitution as illustrated by Scheme 6. In this scheme, a dione of type 6a, such as 1-(4-chlorophenyl)-2-(4-pyrimidinyl)-2-ethandione is treated with an aldehyde such as ethoxypropionaldehyde, ammonium acetate and acetic acid at about 70 °C to reflux for several hours. The desired compound is isolated from this mixture to give a compound of the type 6b. This scheme may be used to produce compounds of the invention where n is 0, q is 1-9 and X is H, phthalimido and C₁₋₅alkoxy.

SCHEME 6



In order to produce compounds of the invention where R₃ is other than hydrogen or SEM, the final products of Schemes 1-6 may be treated with a base such as NaH, *n*-BuLi or K₂CO₃ in an inert solvent such as DMF or THF at room temperature over 15 minutes to several hours. The resulting anion may be treated with an appropriate alkylating or acylating agent. For example, to produce compounds of the invention where R₃ is arylcarbonyl, A is sulfur and X is pentyl, compounds of the type 1b may be treated with NaH, followed by benzoyl chloride.

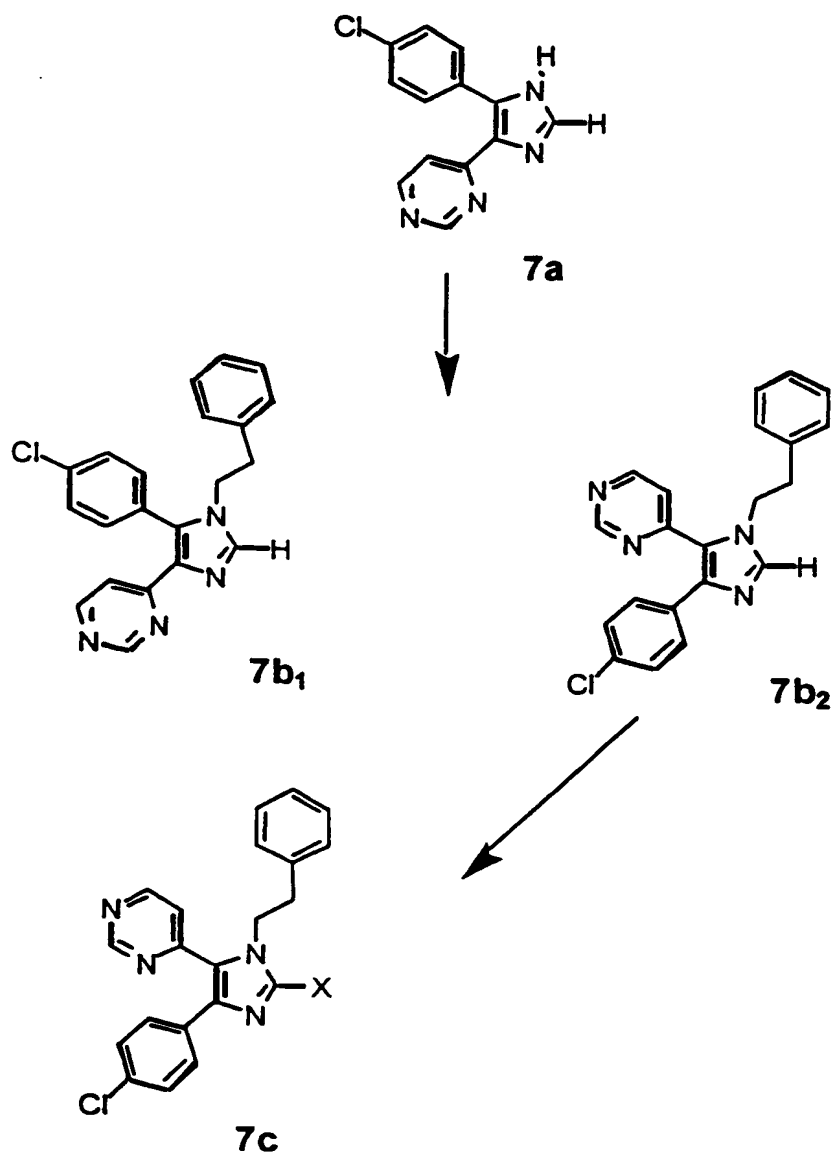
In order to produce the compounds of the invention where n is 0, q is 0 and X is halogen, Scheme 7 may be used. The starting material for the scheme is a 4,5-disubstituted imidazole of the type 7a. Substituted imidazoles may be prepared following known procedures and the substituents R₁ and R₂ of the compounds of the invention are determined by the substituents of intermediate 7a. Intermediate 7a is treated with a base, such as NaH and an

inert solvent such as DMF at room temperature for about 30 min to 1 h. Once anion formation is complete, an alkylating agent is added such as phenethyl chloride and the reaction mixture is stirred at about 60-100 °C for about 2-4 h to give intermediates 7b₁ and 7b₂. These intermediates are separated at this

- 5 stage to allow for the formation of final products with one predominate isomer. Although the final products may be separated, the separation of 7b₁ and 7b₂ leads to higher yields of products.

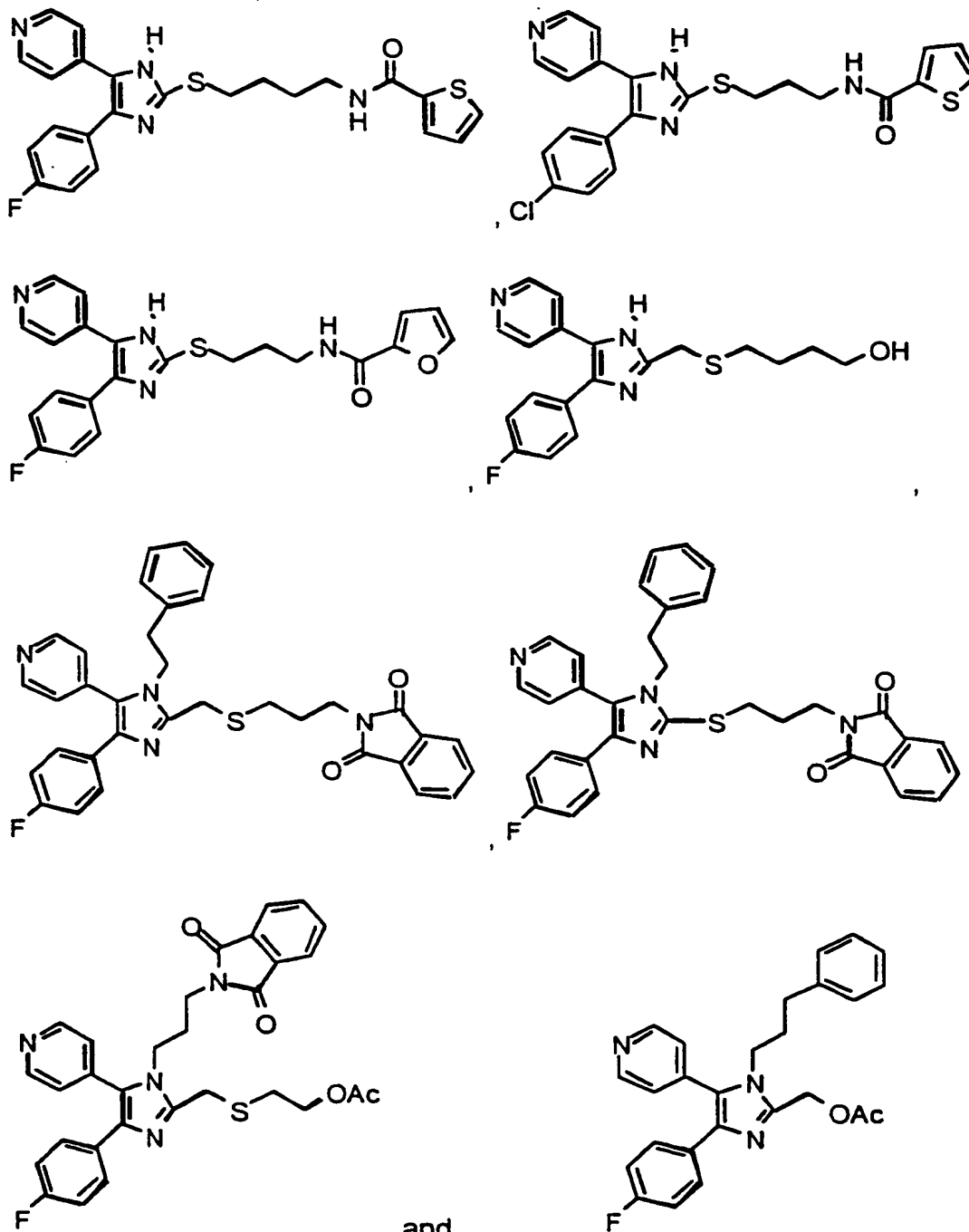
- 10 Intermediate 7b₂ is treated with a strong base such as LDA in an inert solvent such as THF at -78 °C for about 30 min. A source of halogen atoms such as iodine or bromine is added to the formed anion and this mixture is allowed to warm to ambient temperature over 30 min to 1 h to give intermediate 7c where X is iodine.

SCHEME 7



Although the claimed compounds are useful as inhibitors of TNF- α and IL-1, some compounds are more active than others and are either preferred or particularly preferred.

The preferred compound of Formula I include:



5 The particularly preferred "R₁"s are phenyl or substituted phenyl where the phenyl substituents are halogen and nitrile.

The particularly preferred "R₂"s are pyrid-4-yl, pyrimidin-4-yl and 2-butyl-pyrid-4-yl.

10 The particularly preferred "R₃"s are hydrogen, SEM, C₁₋₅alkyl phenylC₁₋₅alkyl, and substituted phenylC₁₋₅alkyl.

The particularly preferred "q"s are 0-6.

The particularly preferred "X"s are hydrogen, hydroxy, nitrile, C₁₋₅alkyl, phthalimido, amido, substituted amido, C₁₋₅alkylsulfonyl, hydroxyC₁₋₅alkylsulfonyl, phenylsulfonyl, substituted phenylsulfonyl, substituted amido, substituted
5 sulfonamido, C₁₋₅alkoxycarbonyloxy, and C₁₋₅alkyl.

Compounds of Formula I may be used in pharmaceutical compositions to treat patients (humans and other primates) with disorders related to the overproduction of inflammatory cytokines, particularly TNF- α . The preferred route is oral administration, however compounds may be administered by intravenous
10 infusion or topical administration. Oral doses range from about 0.05 to 100 mg/kg, daily. Some compounds of the invention may be orally dosed in the range of about 0.05 to about 50 mg/kg daily, while others may be dosed at 0.05 to about 20 mg/kg daily. Infusion doses can range from about 1.0 to 1.0×10^4 μ g/kg/min of inhibitor, admixed with a pharmaceutical carrier over a period ranging from
15 several minutes to several days. For topical administration compounds of Formula I may be mixed with a pharmaceutical carrier at a concentration of about 0.1 to about 10% of drug to vehicle.

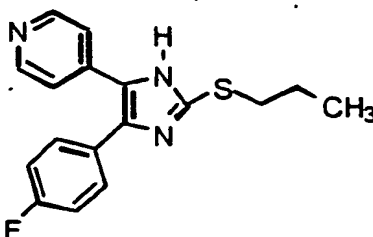
The pharmaceutical compositions can be prepared using conventional pharmaceutical excipients and compounding techniques. Oral dosage forms
20 may be elixers, syrups, capsules tablets and the like. Where the typical solid carrier is an inert substance such as lactose, starch, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, mannitol and the like; and typical liquid oral excipients include ethanol, glycerol, water and the like. All excipients may be mixed as needed with disintegrants, diluents, granulating
25 agents, lubricants, binders and the like using conventional techniques known to those skilled in the art of preparing dosage forms. Parenteral dosage forms may be prepared using water or another sterile carrier.

Typically the compounds of Formula I are isolated and used as free bases, however the compounds may be isolated and used as their pharmaceutically
30 acceptable salts. Examples of such salts include hydrobromic, hydroiodic, hydrochloric, perchloric, sulfuric, maleic, fumaric, malic, tartatic, citric, benzoic, mandelic, methanesulfonic, hydroethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic and saccharic.

In order to illustrate the invention the following examples are included.
35 These examples do not limit the invention. They are only meant to suggest a method of practicing the invention. Those skilled in the art may find other methods of practicing the invention, which are readily apparent to them. However those methods are deemed to be within the scope of this invention.

SYNTHETIC EXAMPLES

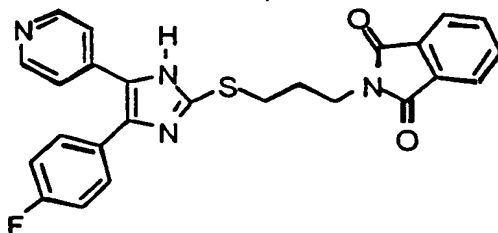
Exempl 1



5(4)-(4-Fluorophenyl)-2-(1-propylthio)-4(5)-(4-pyridyl)-5(4)-imidazole
Cpd. 1

- 5 A slurry of 4-(4-fluorophenyl)-2-mercapto-5-(4-pyridyl)imidazole (0.52 g, 1.92 mmol; Lantos et al *Journal of Organic Chemistry*, 1988, 53, 4223-27), 95%NaH (48 mg, 1.92 mmol) and DMF (20 mL) was stirred under N₂ for 30 min at room temperature. 1-Iodopropane (0.19 mL, 1.92 mmol) was added and the resulting solution was stirred at room temperature for 20h. The reaction mixture
- 10 was poured into ice/H₂O (100 mL) and the resulting yellow solid was filtered and washed with H₂O. This solid was recrystallized from MeOH/H₂O (20:5) to give compound 1 as a yellow solid: mp 222-27 °C; MS (Cl⁺) 314 (M⁺).

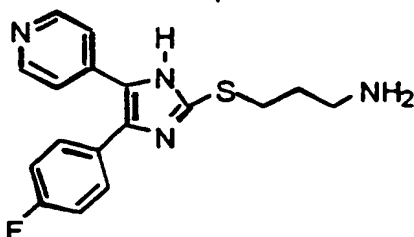
Example 2



- 15 5(4)-(4-Fluorophenyl)-2-(3-phthalimidoprop-1-ylthio)-4(5)-(4-pyridyl)-imidazole
Cpd. 2

- N-(3-bromopropyl)phthalimide (1.02 g, 3.8 mmol) and 60% NaH (0.152 g) were added to a solution of 4-(4-fluorophenyl)-2-mercapto-5-(4-pyridyl)-imidazolethione (1.03 g, 3.80 mmol) and the resulting mixture was stirred at room
- 20 temperature for 1h. The mixture was poured into ice/H₂O and the resulting solid was washed with water and dried to give compound 2 as a solid: mp 241-43 °C; MS 459 (MH⁺).

Example 3



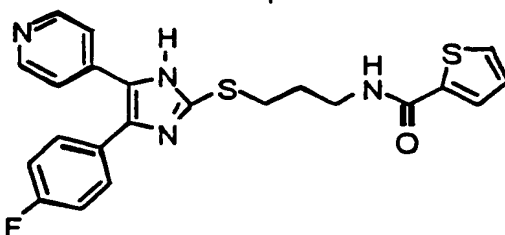
2-(3-Aminoprop-1-ylthio)-5(4)-(4-fluorophenyl)-4(5)-(4-pyridyl)-imidazole

Cpd. 3

- 5 55% Hydrazine (1.1 mL) was added to a solution of compound 2 (4.40 g, 9.60 mmol) in MeOH (??) and this mixture was heated at reflux for 4 h. The resulting mixture was concentrated in vacuo and triturated with 1N NaOH. The solid precipitate was filtered, washed with water and dried to give compound 3 as a solid: MS 329 (MH⁺)

10

Example 4

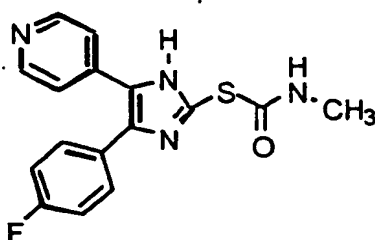


5(4)-(4-Fluorophenyl)-2-(3-(thien-2-ylamido)prop-1-ylthio)-
4(5)-(4-pyridyl)-imidazole

Cpd. 4

- 15 Sodium bicarbonate (0.42 g) and thiophenecarbonyl chloride (0.28 mL, 2.50 mmol) were added to a solution of compound 3 (0.75 g, 2.27 mmol) in DMF (6 mL) under N₂ at room temperature. This mixture was stirred for 45 min and poured into ice/H₂O. The resulting solid was filtered, washed with H₂O and dried in vacuo to give compound 4 as a solid: mp 172-75 °C; MS 439 (MH⁺).

Example 5

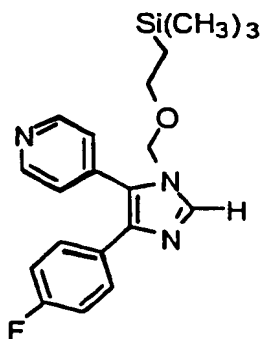


5(4)-(4-Fluorophenyl)-2-(N-methylaminocarbonylthio)
-4(5)-(4-pyridyl)-imidazole

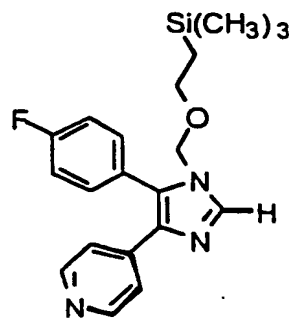
Cpd. 5

95% Sodium Hydride (32 mg, 1.3 mmol) and methyl isocyanate (0.77 mL, 1.30 mmol) were added successively to a solution of 4-(4-fluorophenyl)-2-mercapto-5-(4-pyridyl)imidazole (350 mg, 1.30 mmol) and this mixture was stirred at room temperature for 2h. The resulting mixture was poured into H₂O and the solid precipitate was filtered, washed with H₂O and dried in vacuo to give compound 5 as a solid: mp >275 °C; MS 272 (M-CONHCH₃).

Example 6



Cpd. 6a

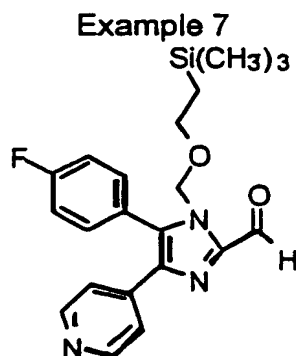


Cpd. 6b

4-(4-Fluorophenyl)-5-(4-pyridyl)-1-(2-(trimethylsilyl)ethoxymethyl)-
imidazole Cpd. 6a

5-(4-Fluorophenyl)-4-(4-pyridyl)-1-(2-(trimethylsilyl)ethoxymethyl)-
imidazole Cpd. 6b

60% Sodium Hydride (0.92 g, 23 mmol) was added to a stirred solution of 5(4)-(4-fluorophenyl)-4(5)-(4-pyridyl)-imidazole (5.50 g, 23 mmol) in DMF under N₂. 2-(Trimethylsilyl)ethoxymethyl chloride (4.07 mL, 23 mmol) was added after 15 min and the resulting mixture was stirred for 3 h, poured into H₂O, dried (MgSO₄) and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel using ethyl acetate as an eluent. The less polar isomer crystallized to give compound 6a: mp 111-13 °C; MS 370 (MH⁺). The more polar isomer crystallized to give compound 6b: mp 62-64 °C; MS 370 (MH⁺).



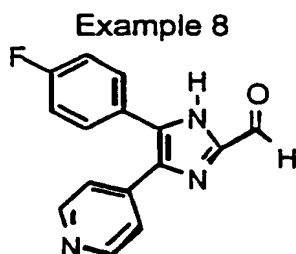
5-(4-Fluorophenyl)-4-(4-pyridyl)-1-(2-(trimethylsilyl)ethoxymethyl)-
2-imidazole carboxaldehyde

5

Cpd. 7

n-Butyl lithium (1.6 N, 13 mL, 21.0 mmol) was added to a stirred solution of compound 6b (7.10 g, 19.2 mmol) in THF at -77 to -78 °C. This mixture was stirred for 15 min, DMF (2 mL, 26 mmol) was added and the resulting mixture was stirred at ambient temperature for about 1h. The reaction was quenched with H₂O, extracted with ethyl acetate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane as an eluent to give compound 7 as a solid: mp 42-45 °C; MS 398 (MH⁺).

10



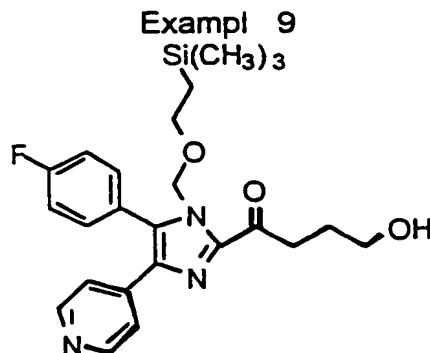
15

5(4)-(4-Fluorophenyl)- 4(5)-(4-pyridyl)-2-imidazole carboxaldehyde

Cpd. 8

1N HCl (20 mL) was added to a solution of compound 7 (1.60 g) in EtOH (20 mLs). This mixture was stirred for 30 min, neutralized with NaHCO₃ and poured into H₂O. The solid precipitate was filtered and dried to give the title compound as a solid: mp 233-43 °C (dec.); MS 268 (MH⁺).

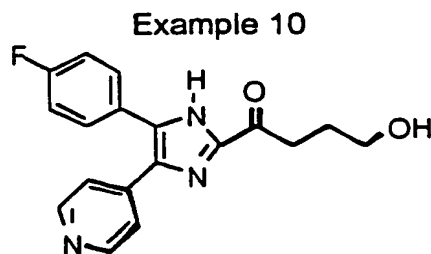
20



4-Hydroxy-1-[5-(4-fluorophenyl)-4-(4-pyridyl)-1-(2-(trimethylsilyl)ethoxymethyl)
imidazol-2-yl]butanone

Cpd. 9

n-Butyl lithium (1.6 N, 3.5 mL, 5.6 mmol) was added to a stirred solution of compound 6b (3.5 mL, 5.78 mmol) in THF at -77 to -78 °C. This mixture was stirred for 15 min, α -butyrolactone (2 mL, 26 mmol) was added and the resulting mixture was stirred to ambient temperature. The reaction was quenched with H₂O, extracted with ethyl acetate and concentrated in vacuo. The residue was purified by column chromatography on silica gel using methylene chloride/MeOH 19:1, as an eluent to give compound 9 as a solid: mp 109.5-110.5°C; MS 456 (MH⁺).

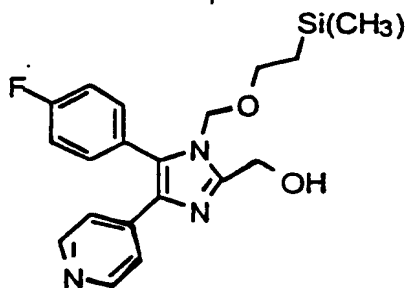


4-Hydroxy-1-[5-(4-fluorophenyl)- 4-(4-pyridyl)-imidazol-2-yl]butanone

Cpd. 10

Cpd. 9 (8.20 g, 1.8 mmol) was heated at reflux in 1N HCl for 1h. The mixture was cooled and neutralized with sodium bicarbonate. The resulting solid precipitate was filtered and washed with H₂O to give compound 10 as a solid: mp 205-07 °C.

Example 11



5-(4-Fluorophenyl)-2-hydroxymethyl-4-(4-pyridyl)
1-(2-(trimethylsilyl)ethoxymethyl) imidazole

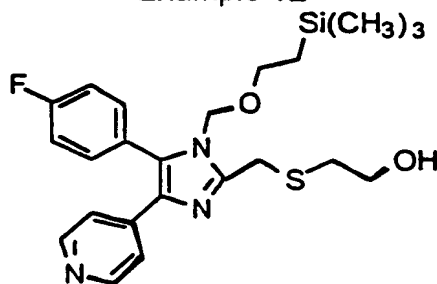
5

Cpd. 11

10% Palladium on carbon (3.0 g) was added to a solution of compound 7 (3.93 g, 9.89 mmol) in MeOH. This mixture was shaken under H₂ (40 psi) for 1h, filtered and concentrated in vacuo to give the title compound as a solid: mp 169-71 °C, MS 400 (MH⁺).

10

Example 12



5-(4-Fluorophenyl)-2-[4-hydroxy-2-thiabut-1-yl]-4-(4-pyridyl)-
1-(2-(trimethylsilyl)ethoxymethyl)imidazole

Cpd. 12

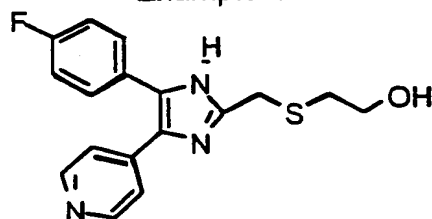
15

Triphenylphosphine (3.77 g, 14.4 mmol) and CCl₄ (1.39 mL, 14.4 mmol) were added to a solution of compound 11 (2.87 g, 7.18 mmol) in acetonitrile (70 mL) and the resulting mixture was stirred for 4 h. 2-Mercaptoethanol (2.52 mL, 35.9 mmol) and NaOH (2.44 g, 35.9 mmol) were added to the reaction and the resulting mixture was stirred for another 18 h and concentrated in vacuo. The

20

residue was partitioned between water and ethyl acetate and the organic layer was concentrated in vacuo. This residue was purified by column chromatography on silica gel using ethyl acetate/hexane (1:1) to give the title compound as a solid: mp 74-76 °C, MS 460 (MH⁺).

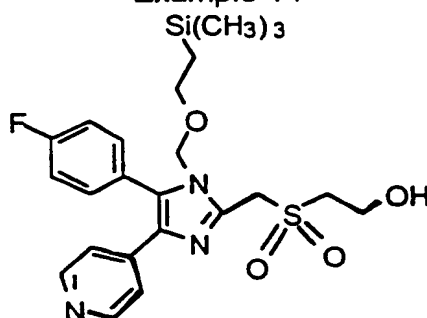
Example 13



5-(4-Fluorophenyl)-2-[4-hydroxy-2-thiabut-1-yl]-4-(4-pyridyl)-imidazole
Cpd. 13

5 A mixture of compound 12 (260 mg, 0.566 mmol) and 1N HCl (10 mL) was heated to 100 °C for 8h. The resulting mixture was neutralized with sodium bicarbonate and the solid precipitate was filtered, washed with H₂O and dried to give the title compound as a solid: mp 227-29 °C; MS 330 (MH⁺).

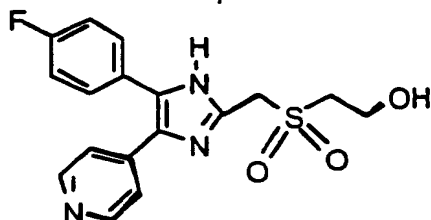
Example 14



5-(4-Fluorophenyl)-2-[4-hydroxy-2-sulfonyl-but-1-yl]-4-(4-pyridyl)-
1-(2-(trimethylsilyl)ethoxymethyl)imidazole
Cpd. 14

10 A solution of oxone (2.00 g, 3.25 mmol) in H₂O (100 mL) was added to a stirred solution of compound 12 (0.50 g, 1.09 mmol) in MeOH (100 mL). This mixture was stirred for 4 h at ambient temperature concentrated in vacuo and extracted with methylene chloride. The combined organic layer was dried and concentrated to a residue. This residue was purified by column chromatography using methylene chloride : MeOH (19:1) as an eluent to give the title compound
15 as a solid: mp 45-48 °C; MS 492(MH⁺).
20

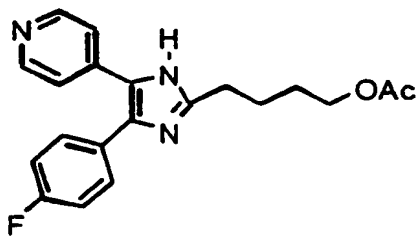
Example 15



5-(4-Fluorophenyl)-2-[4-hydroxy-2-sulfonyl-but-1-yl]-4-(4-pyridyl)-imidazole
Cpd. 15

- 5 A solution of compound 14 (343 mg, 0.698 mmol) and 1N HCl was stirred at 90 °C for 2 h. This mixture was neutralized with sodium bicarbonate and the resulting solid precipitate was washed with water to give the title compound: mp 232-237 °C; MS 362 (MH⁺).

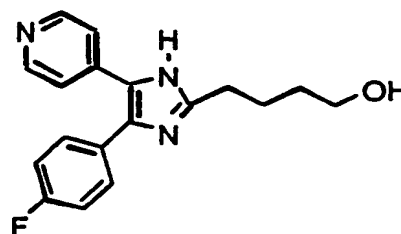
Example 16



16a

4-[5(4)-(4-Fluorophenyl)-4(5)-(4-pyridyl)imidazol-2-yl]butyl acetate

Cpd. 16a



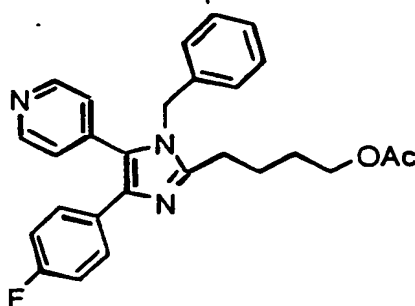
16b

4-[5(4)-(4-Fluorophenyl)-4(5)-(4-pyridyl)imidazol-2-yl]butanol

Cpd. 16b

- 15 5-Hydroxy pentanal (0.97 mL) and ammonium acetate (5.60 g, 72.7 mmol) were added to a solution of 1-(4-fluorophenyl)-2-(4-pyridyl)-1,2-ethandione (2.08 g, 9.08 mmol) in acetic acid (50 mL) and the mixture was heated at reflux for 1 h. The resulting mixture was cooled to about 0 °C and the ammonium hydroxide was
- 20 added until the mixture reached a pH of 8. This mixture was extracted with ethyl acetate and purified on silica gel using methylene chloride : methanol (9:1) as an eluent, where compound 12a was isolated as the least polar product: MS 354 (MH⁺) and compound 12b was isolated as the most polar product: mp 213-214.5 °C, MS 312 (MH⁺).

Example 17



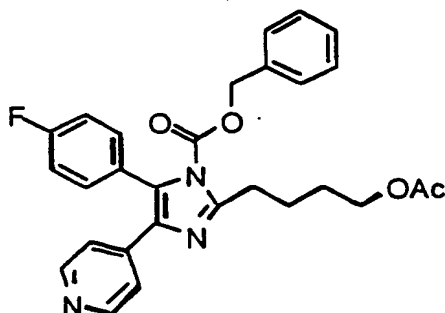
Cpd. 17

4-[1-Benzyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]butyl acetate

Cpd. 17

Sodium hydride (.112 g, 2.88 mmol) was added to a solution of compound 16a (1.00 g, 2.80 mmol) in DMF (50 mL) and the mixture was stirred for 30 min. Benzyl bromide (0.34 mL, 2.80 mmol) was added and this mixture was stirred for 2.5 h at ambient temp and poured into water. The aqueous mixture was extracted with ethyl acetate and the combined organic extracts were concentrated in vacuo and purified by column chromatography using ethyl acetate as an eluent to give compound 17 as an oil: MS 444 (MH⁺).

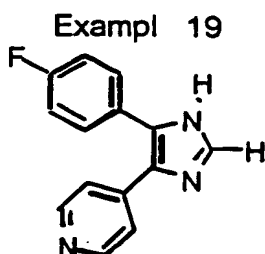
Example18



**4-[1-Benzyloxycarbonyl-4-(4-fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]-
butyl acetate**

Cpd. 18

Triethylamine (0.4 mL) and benzyl chloroformate (0.20 mL, 1.40 mmol) was added to a solution of compound 16a. This mixture was stirred for 2 h at ambient temperature, concentrated in vacuo and partitioned between methylene chloride and H₂O. The organic extracts were concentrated in vacuo to give compound 18 as a solid: mp 97-101 °C; MS 488 (MH⁺).



5(4)-(4-Fluorophenyl)-4(5)-(4-pyridyl)imidazole

Cpd. 19

- 5 A solution of selenium dioxide (4.82 g, 43.4 mmol) in H₂O (20 mL) was added to a solution of 1-(4-fluorophenyl)-2-(4-pyridyl)-2-ethanone (9.33 g, 43.4 mmol) in dioxane (100 mL) and the resulting mixture was heated at reflux for 2 h. This mixture was concentrated in vacuo, triturated with ethyl acetate and filtered. The residue was purified by column chromatography using ethyl acetate/ hexane
- 10 (1:1) as an eluent to give 1-(4-fluorophenyl)-2-(4-pyridyl)-1,2-ethandione. A mixture of ammonium acetate (25.25 g, 0.328 mol) and hexamethylenetetraamine (9.18 g, 65.5 mmol) was added to a solution of the isolated dione dissolved in acetic acid (150 mL). This mixture was stirred at 80 °C for 2 h, poured into concentrated ammonium hydroxide (200 mL) and the resulting precipitate was
- 15 filtered, washed with H₂O and dried to give the title compound as a solid: mp 242-44.3 °C; MS 240 (MH⁺).

BIOLOGICAL EXAMPLES

- One of the biological activities of the compounds of the invention was demonstrated by in vitro and in vivo assays. As discussed previously, agents
- 20 which inhibit the activity of the enzyme p38, inhibit the production of the inflammatory cytokines TNF- α and IL-1. Compounds of the invention were measured for their ability to inhibit the activity of p38 by the following in vitro assay.

Example 20

- 25 A solution (38 μ L) of purified recombinant p38 (where the amount of enzyme was determined empirically considering the linear range of the assay and the acceptable signal to noise ratio; 6xHis-p38 expressed in E. coli), myelin basic protein substrate (also determined empirically), a buffer of pH 7.5 (Hepes:25 mM, MgCl₂:10 mM, MnCl₂:10 mM) were added to 92 wells of a 96-
- 30 well round bottom polypropylene plate. The remaining wells were used for control ("CTRL") and background ("BKG"). The CTRL was prepared with the enzyme, substrate buffer and 2% DMSO, and the BKG was prepared with substrate buffer and 2% DMSO. A solution (12 μ L) of the test compound in

DMSO (compounds were diluted to 125 μ M in 10% DMSO/H₂O and assayed at 25 μ M where the final DMSO concentration was 2%) was added to the testing wells. The ATP/³³P-ATP solution (10 μ L: containing 50 μ M unlabeled ATP and 1 μ Ci ³³P-ATP) was added to all wells and the completed plates were
5 mixed and incubated at 30 °C for 30 min. Ice-cold 50 % TCA/10 mM sodium phosphate (60 μ L) were added to each well and the plates were kept on ice for 15 min. The contents of each well were transferred to the wells of a 96-well filterplate (Millipore, MultiScreen-DP) and the filterplate was placed on a vacuum manifold, fitted with a waste collection tray. The wells were washed
10 five times with 10% TCA/10 mM sodium phosphate (200 μ L) under vacuum. MicroScint-20 scintillant was added, the plates were sealed using Topseal-S sheets and counted in a Packard TopCount scintillation counter using a ³³P liquid program with color quench correction, where the output is in color quench-corrected cpm. The % inhibition of the test compounds was calculated
15 by the following formula: % inhibition = [1 - (sample -BKG)/(CTRL-BKG)] x 100. This data is shown in Table A.

Although compounds were initially tested at 25 μ M, if warranted the compounds were tested at 4-fold increments above and below that concentration. In addition, IC₅₀s were calculated for some compounds using
20 the Deltagraph 4-parameter curve fitting program.

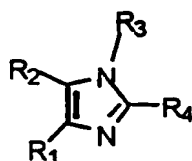
Example 21

In addition to the enzyme assay, the compounds of the invention were tested in an in vitro whole cell assay using peripheral blood mononuclear cells ("PBMC") which were obtained from human blood as follows. Freshly obtained
25 venous blood was anticoagulated with heparin, diluted with an equal volume of phosphate buffered saline ("PBS") and placed in a sterile tube or other container. Aliquots (30 mL) of this mixture were transferred to centrifuge tubes which were underlaid with Ficoll-Hypaque (15 mL). The prepared tubes were centrifuged at 400 x g without braking for 30 min at room temperature.
30 Approximately 1/2 to 2/3 of the platelet layer above the mononuclear cell band was removed with a pipet. The majority of the mononuclear cell layer was carefully removed using a pipet and these PBMCs were diluted with PBS and spun at 600 x g for 15 min. The resulting PBMCs were washed with another portion of PBS and spun at 400 x g for 10 min at room temperature. The
35 recovered pellets were diluted in low endotoxin RPMI / 1% FCS culture medium and gave a cell concentration of 0.5-2.0 X 10⁶ PMBC/ mL. A small volume of the suspension was removed for counting on a hemocytometer and the remaining preparation was centrifuged at 200 x g for 15 min at room

temperature. The recovered pelleted PMBC were resuspended in RPMI / 1% FCS to a concentration of $1.67 \times 10^6/\text{mL}$.

To run the assay, the PBMC suspension (180 μL) was transferred to duplicate wells of a 96-well flat-bottom microtiter plate and incubated for 1 h at 37 °C. A solution of test compound (10 μL ; prepared at 20 x the desired final concentration) was added to each well and the plate was incubated for 1 h at 37 °C. A solution (10 μL) of LPS in RPMI / 1% FCS (200 ng/mL) was added and the wells were incubated overnight at 37 °C. The supernate (100 μL) was removed from each well and diluted with RPMI / 1% FCS (400 μL). The samples were analyzed for TNF- α using a commercial ELISA kit (Genzyme). This data is shown in Table A. In addition to the biological data, the synthetic schemes which may be used to prepare the compounds are listed. Since imidazoles which are unsubstituted at the 1-position are subject to tautomerization, the substituents listed for R_1 and R_2 are interchangeable when R_3 is hydrogen.

TABLE A



	Cpd.#	R_1	R_2	R_3	R_4	CPSB $\text{IC}_{50} \mu\text{m}$	TNF- α $\text{IC}_{50} \text{ nm}$	Sch eme
20	1	4-F-Ph	4-pyr	H	S-(CH ₂) ₂ CH ₃	0.68		1
	2	4-F-Ph	4-pyr	H	S-(CH ₂) ₃ PHT	0.79-1.8	1000	1
	3	4-F-Ph	4-pyr	H	S-(CH ₂) ₃ NH ₂	26% @ 20 μm		1
	4	4-F-Ph	4-pyr	H	S-(CH ₂) ₃ NHC(O)- 2-thienyl	1.25	10	2
25	5	4-F-Ph	4-pyr	H	SC(O) NHCH ₃	81% @ 20 μm		1
	8	4-F-Ph	4-pyr	H	C(O)H	0.8	140	3
	9	4-pyr	4-F-Ph	SEM	C(O)(CH ₂) ₃ OH		>10000	3
	10	4-F-Ph	4-pyr	H	C(O)(CH ₂) ₃ OH		400	3
	13	4-F-Ph	4-pyr	H	CH ₂ S(CH ₂) ₂ OH		80	4
30	15	4-F-Ph	4-pyr	H	CH ₂ SO ₂ (CH ₂) ₂ OH		40	5
	16a	4-pyr	4-F-Ph	H	(CH ₂) ₄ OAc	1.42		6
	16b	4-F-Ph	4-pyr	H	(CH ₂) ₄ OH	1.59	10	6

	17	4-F-Ph	4-pyr	CH ₂ PH	(CH ₂) ₄ OAc	2.63	500	6
	18	4-pyr	4-F-Ph	CO ₂ CH ₂ Ph	(CH ₂) ₄ OAc	10% @ 5 μm		6
	20	4-F-Ph	4-pyr	H	S(CH ₂) ₂ CH(OCH ₂ CH ₃) ₂	2.0		1
	21	4-F-Ph	4-pyr	H	SH	1.9		1
5	22	4-F-Ph	4-pyr	H	SCH(CH ₃) ₂	0.47		1
	23	4-F-Ph	4-pyr	H	SCH ₂ -cyclopropyl	1.0-1.8		1
	25	4-F-Ph	4-pyr	H	S(CH ₂) ₂ PHT	52% @ 5 μm	500	1
	26	4-F-Ph	4-pyr	H	S(CH ₂) ₃ NHC(O)Ph	2.18	100	2
	27	4-F-Ph	4-pyr	H	S(CH ₂) ₄ PHT	2.46	2000	1
10	28	4-F-Ph	4-pyr	H	S-(CH ₂) ₃ NH- C(O)-1-naphthyl	1.25	97	2
	29	4-F-Ph	4-pyr	H	S-(CH ₂) ₃ NH- C(O)-2-furanyl	91% @ 20 μm	112	2
	30	4-F-Ph	4-pyr	H	S-(CH ₂) ₃ NH- S(O) ₂ -Ph	92% @ 20 μm	100	2
15	31	4-F-Ph	4-pyr	H	S-(CH ₂) ₃ NH- C(O)-2-naphthyl		275	2
	32	4-F-Ph	4-pyr	H	S(CH ₂) ₃ -NHS(O) ₂ CH ₃		150	2
	33	4-F-Ph	4-pyr	H	CH ₂ S(CH ₂) ₂ PHT		200	4
20	34	4-F-Ph	4-pyr	H	S(CH ₂) ₃ NHC(O)CH ₃		200	
	35	4-F-Ph	4-pyr	H	CH ₂ S(CH ₂) ₂ CH ₃		30	4
	36	4-pyr	4-F-Ph	SEM	CH ₂ OH	6% @ 5 μm		
	37	4-F-Ph	4-pyr	H	SCH ₂ CHCH ₂	0.75		1
	38	4-F-Ph	4-pyr	H	SCH ₂ CN	0.4		1
25	39	4-F-Ph	4-pyr	H	SCH ₂ CH ₃	0.4		1
	40	4-F-Ph	4-pyr	H	S(CH ₂) ₃ CH ₃	0.28-0.7		1
	41	4-F-Ph	4-pyr	H	S(CH ₂) ₉ CH ₃		>10,000	1
	42	4-pyr	4-F-Ph	CH ₂ Ph	(CH ₂) ₄ OAc	2% @ 5 μm		6
	43	4-pyr	4-F-Ph	CH ₂ Ph	(CH ₂) ₄ PHT	8% @ 5 μm		6
30	44	4-F-Ph	4-pyr	SEM	(CH ₂) ₄ OAc	74% @ 20	150	6
	45	4-pyr	4-F-Ph	SEM	(CH ₂) ₄ OAc	8% @ 20 μm	-inactive	6
	46	4-pyr	4-F-Ph	SEM	(CH ₂) ₄ OH	9% @ 20 μm	inactive	6
	47	4-pyr	4-F-Ph	H	(CH ₂) ₄ PHT		283	6
	48	4-F-Ph	4-pyr	CH ₂ Ph	(CH ₂) ₄ PHT		1750	6
35	49	4-F-Ph	4-pyr	H	CH ₂ OH		250	4
	50	4-F-Ph	4-pyr	(CH ₂) ₃ PHT	(CH ₂) ₄ OAc		150	6
	51	4-F-Ph	4-pyr	(CH ₂) ₃ PHT	(CH ₂) ₄ OH		175	6
	52	4-pyr	4-F-Ph	(CH ₂) ₃ PHT	(CH ₂) ₄ OH		200	6

5	53	4-F-Ph	4-pyr	(CH ₂) ₃ PHT	CH ₂ O(CH ₂) ₃ PHT	175	4
	54	4-pyr	4-F-Ph	(CH ₂) ₃ PHT	CH ₂ O(CH ₂) ₃ PHT	200	4
	55	4-pyr	4-F-Ph	(CH ₂) ₃ PHT	CH ₂ OH	1250	4
	56	4-F-Ph	4-pyr	(CH ₂) ₃ PHT	CH ₂ OH	30	4
	57	4-pyr	4-F-Ph	SEM	CH ₂ SO ₂ C ₃ H ₇	5000	5
10	58	4-F-Ph	4-pyr	(CH ₂) ₃ PHT	CH ₂ O CH ₃	75	6
	59	4-pyr	4-F-Ph	H	CH ₂ SO ₂ C ₃ H ₇	55	5
	60	4-pyr	4-F-Ph	(CH ₂) ₃ PHT	CH ₂ OCH ₃	400	6
	61	4-F-Ph	4-pyr	(CH ₂) ₃ PHT	(CH ₂) ₂ OC ₂ H ₅	200	6
	62	4-F-Ph	4-pyr	(CH ₂) ₃ PHT	CH ₃	362	6
15	63	4-pyr	4-F-Ph	(CH ₂) ₃ PHT	CH ₃	17	6
	64	4-F-Ph	4-pyr	(CH ₂) ₃ PHT	C ₂ H ₅	80.0	6
	65	4-pyr	4-F-Ph	(CH ₂) ₃ PHT	C ₂ H ₅	20.0	6
	66	4-F-Ph	4-pyr	(CH ₂) ₃ Ph	C ₂ H ₅	6	6
	67	4-pyr	4-F-Ph	(CH ₂) ₃ Ph	C ₂ H ₅	300	6
20	68	4-F-Ph	4-pyr	(CH ₂) ₃ Ph	CH ₃	1.5	6
	69	4-pyr	4-F-Ph	(CH ₂) ₃ Ph	CH ₃	100	6
	70	4-pyr	4-F-Ph	(CH ₂) ₃ PHT	H	500	7
	71	4-F-Ph	4-pyr	(CH ₂) ₃ PHT	H	39	7
	72	4-pyr	4-F-Ph	(CH ₂) ₄ PHT	H	300	7
25	73	4-F-Ph	4-pyr	(CH ₂) ₄ PHT	H	500	7
	74	4-F-Ph	4-pyr	(CH ₂) ₃ Ph	Br	200	7
	75	4-F-Ph	4-pyr	(CH ₂) ₃ Ph	I	3	7
	76	4-pyr	4-F-Ph	(CH ₂) ₄ PHT	I	800	7
	77	4-F-Ph	4-pyr	(CH ₂) ₄ PHT	I	445	7
30	78	4-F-Ph	4-(2-butyl)pyr	(CH ₂) ₃ Ph	CH ₂ OH	450	4
	79	4-pyr	4-F-Ph	CH ₂ COC ₂ H ₅	H	600	
	80	4-F-Ph	4-pyr	CH ₂ COC ₂ H ₅	H	200	
	81	4-pyr	4-F-Ph	(CH ₂) ₃ -3-pyr	H	500	
	82	4-F-Ph	4-pyr	(CH ₂) ₃ -3-pyr	H	20	
	83	4-pyr	4-F-Ph	(CH ₂) ₃ -4-pyr	H	1000	
	84	4-F-Ph	4-pyr	(CH ₂) ₃ -4-pyr	H	10	
	85	4-pyr	4-F-Ph	(CH ₂) ₂ -OPh	H	2000	
	86	4-F-Ph	4-pyr	(CH ₂) ₂ -OPh	H	40	

Example 22

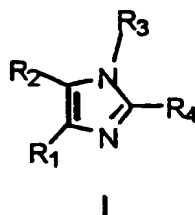
The IL-1 B modulating activity of compounds of the invention was determined by the following in vitro assay. Plastic-adherent cells were prepared from PBMC. Briefly, PBMCs were added to the wells of a 96-well plate as above, incubated for 1 h at 37 °C, and the adherent cells prepared by gently resuspending the non-adherent cells with a pipetor, removing and discarding them and gently washing the wells 3 times with 200 µL culture medium. Additional culture medium (180 µL) was added to the wells after the final wash. Compound addition, LPS stimulation, incubation and supernate harvest were as for TNF-α. Supernatant was assayed for interleukin-1β using a commercial ELISA (Genzyme). Compounds 10, 28 and 59 inhibited the production of IL-1B at IC₅₀s of 800, 86 and 350 nM, respectively.

Example 23

The ability of the compounds of Formula I to inhibit LPS induced TNF-α production was demonstrated in the following in vivo rodent assays. Mice (BALB / cJ females, Jackson Laboratories) or rats (Lewis males, Charles River) were fasted for 30 min prior to oral dosing with 5-10 mL/kg of test compound at 5-50 mg/kg. Thirty minutes after dosing, the animals were injected intraperitoneally with LPS at 1 mg/kg and returned to their cages for 1 h. Animals were anesthetized by CO₂, exsanguinated by cardiac puncture and whole blood collected (0.1-0.7 mL). The blood was allowed to clot and serum was transferred to a centrifuge tube. This sample was centrifuged, serum was collected, aliquoted and frozen at -80 °C. Samples were tested by commercial ELISAs for TNF-α (Endogen for mouse TNF-α and Biosource for rat TNF-α). Compounds 15 and 56 inhibited TNF-α production in the mouse at 88% and 37% respectively at a dose of 25 mg/kg.

What is claimed is:

1. A compound of Formula I



5 wherein:

R_1 is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or substituted phenyl

10 wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R_2 is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, substituted heteroaryl

15 wherein the substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl and halogen, or substituted phenyl

20 wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R_3 is hydrogen, SEM, C_{1-5} alkoxycarbonyl, aryloxycarbonyl, aryl C_{1-5} alkyloxycarbonyl, aryl C_{1-5} alkyl, phthalimido C_{1-5} alkyl, amino C_{1-5} alkyl, diamino C_{1-5} alkyl, succinimido C_{1-5} alkyl, C_{1-5} alkylcarbonyl, arylcarbonyl, C_{1-5} alkylcarbonyl C_{1-5} alkyl, aryloxycarbonyl C_{1-5} alkyl, heteroaryl C_{1-5} alkyl where the heteroaryl contains 5 to 6 ring atoms, or

25

substituted arylC₁₋₅alkyl

wherein the aryl substituents are independently selected from one or more members of the group consisting of C₁₋₅alkyl, C₁₋₅alkoxy, halogen, amino, C₁₋₅alkylamino, and diC₁₋₅alkylamino;

R₄ is (A)_n-(CH₂)_q-X wherein:

A is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X is selected from the group consisting of hydrogen, hydroxy, halogen, vinyl, ethynyl, C₁₋₅alkyl, C₃₋₇cycloalkyl, C₁₋₅alkoxy, phenoxy, phenyl, arylC₁₋₅alkyl, amino, C₁₋₅alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C₁₋₅alkylaminocarbonyl, phenylaminocarbonyl, arylC₁₋₅alkylaminocarbonyl, C₁₋₅alkylthio, C₁₋₅alkylsulfonyl, phenylsulfonyl, substituted sulfonamido

wherein the sulfonyl, substituent is selected from the group consisting of C₁₋₅alkyl, phenyl, arylC₁₋₅alkyl, thienyl, furanyl, and naphthyl;

substituted vinyl

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted ethynyl

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted C₁₋₅alkyl

wherein the substituents are selected from the group consisting of one or more C₁₋₅alkoxy, trihaloalkyl, phthalimido and amino,

substituted phenyl

wherein the phenyl substituents are independently
selected from one or more members of the group
consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy,

5

substituted phenoxy

wherein the phenyl substituents are independently
selected from one or more members of the group
consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy,

substituted C₁₋₅alkoxy

10

wherein the alkyl substituent is selected from the group
consisting of phthalimido and amino,

substituted arylC₁₋₅alkyl

wherein the alkyl substituent is hydroxyl,

substituted arylC₁₋₅alkyl

15

wherein the phenyl substituents are independently
selected from one or more members of the group
consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy,

substituted amido

20

wherein the carbonyl substituent is selected from the
group consisting of C₁₋₅alkyl, phenyl, arylC₁₋₅alkyl,
thienyl, furanyl, and naphthyl,

substituted phenylcarbonyl

wherein the phenyl substituents are independently
selected from one or members of the group consisting
of C₁₋₅alkyl, halogen and C₁₋₅alkoxy,

25

substituted C₁₋₅alkylthio

wherein the alkyl substituent is selected from the group
consisting of hydroxy and phthalimido,

substituted C₁₋₅alkylsulfonyl

30

wherein the alkyl substituent is selected from the group
consisting of hydroxy and phthalimido,

substituted phenylsulfonyl

wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C₁₋₅alkoxy and trifluoromethyl,

5 with the proviso:

if A is sulfur and X is other than hydrogen, C₁₋₅alkylaminocarbonyl, phenylaminocarbonyl, arylC₁₋₅alkylaminocarbonyl, C₁₋₅alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

10 if A is sulfur and q is 1, then X cannot be C₁₋₂alkyl;

if A is carbonyl and q is 0, then X cannot be vinyl, ethynyl, C₁₋₅alkylaminocarbonyl, phenylaminocarbonyl, arylC₁₋₅alkylaminocarbonyl, C₁₋₅alkylsulfonyl or phenylsulfonyl;

if A is carbonyl, q is 0 and X is H, then R₃ is not SEM;

15 if n is 0 and q is 0, then X cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1 where R₁ is substituted phenyl and R₂ is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-3-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyridazine, triazine, thiazole, and oxazole, pyrazole.

3. The compound of claim 2 where R₁ is 4-fluorophenyl and R₂ is pyridin-4-yl.

4. The compound of claim 3 where R₃ is hydrogen, C₁₋₅alkyl, arylC₁₋₅alkyl, or substituted arylC₁₋₅alkyl.

5. The compound of claim 4 where R₃ is hydrogen or phenylC₁₋₅alkyl.

25 6. The compound of claim 5 where A sulfur, n is 1, and q is 0-6.

7. The compound of claim 6 where X is hydrogen, hydroxy, nitrile, C₁₋₅alkyl, phthalimido, amido, substituted amido, C₁₋₅alkylsulfonyl, hydroxyC₁₋₅alkylsulfonyl, phenylsulfonyl, substituted phenylsulfonyl,

substituted amido, substituted sulfonamido, C₁₋₅alkoxycarbonyloxy, or C₁₋₅alkyl.

8. The compound of claim 5 where n is 0.
9. The compound of 8 where X is hydrogen, hydroxy, nitrile, C₁₋₅alkyl, phthalimido, amido, substituted amido, C₁₋₅alkylsulfonyl, hydroxyC₁₋₅alkylsulfonyl, phenylsulfonyl, substituted phenylsulfonyl, substituted amido, substituted sulfonamido, C₁₋₅alkoxycarbonyloxy, or C₁₋₅alkyl.
10. A compound and pharmaceutically acceptable salts thereof selected from 5(4)-(4-fluorophenyl)-2-(3-(thien-2-ylamido)prop-1-yl)thio-4(5)-(4-pyridyl)-imidazole; 5-(4-fluorophenyl)-2-[hydroxyethylthiamethyl]-4-(4-pyridyl)-imidazole; 5-(4-fluorophenyl)-2-[hydroxyethylsulfonylmethyl]-4-(4-pyridyl)-imidazole; and 4-[5(4)-(4-fluorophenyl)-4(5)-(4-pyridyl)imidazol-2-yl]butanol.
11. A compound and pharmaceutically acceptable salts thereof selected from 5(4)-(4-fluorophenyl)-2-(3-(naphth-1-ylamido)prop-1-yl)thio-4(5)-(4-pyridyl)-imidazole (Cp#28); 5(4)-(4-fluorophenyl)-2-(3-(phenylsulfonamido)prop-1-yl)thio-4(5)-(4-pyridyl)-imidazole (Cp#30); 2-[4-acetoxy-but-1-yl]-5-(4-fluorophenyl)-1-[3-(N-phthalimido)prop-1-yl]-4-(4-pyridyl)-imidazole (Cp#50); 5-(4-fluorophenyl)-2-[hydroxymethyl]-1-[3-(N-phthalimido)prop-1-yl]-4-(4-pyridyl)-imidazole (Cp#56); 5(4)-(4-fluorophenyl)-2-(n-propylsulfonylmethyl)-4(5)-(4-pyridyl)-imidazole (Cp#59); and 2-ethyl-5-(4-fluorophenyl)-1-[3-(N-phthalimido)prop-1-yl]-4-(4-pyridyl)-imidazole (Cp#66).
12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier or diluent.
13. A pharmaceutical composition comprising a compound according to claim 7 and a pharmaceutically acceptable carrier or diluent.
14. A pharmaceutical composition comprising a compound according to claim 9 and a pharmaceutically acceptable carrier or diluent.

15. A method of treating a cytokine mediated disease comprising administering a compound of claim 1 to a mammal at an effective dose.
16. A method of treating a cytokine mediated disease comprising administering a composition of claim 10 to a mammal at an effective dose.
- 5 17. The method of claim 16 where the compound is administered orally and an effective dose is 0.1-100 mg/kg daily.
18. The method of claim 17 where the dose is 0.1-50 mg/kg daily.
19. A method of treating arthritis comprising administering an effective dose of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/US 98/13419

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D233/54 C07D233/84 C07D401/04 A61K31/415 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 14081 A (SMITHKLINE BEECHAM CORP.) 22 July 1993 cited in the application see page 40, line 14 - line 15; claims 1,13,14	1-3,12
X	DE 28 23 197 A (SCHERING AG) 29 November 1979 see claims 16,19,22,25,55,56	1,12
X	DE 28 56 909 A (SCHERING AG) 17 July 1980 see claims 30,33,36,37,42,43	1,12
X	US 4 348 404 A (J. G. WHITNEY) 7 September 1982 see columns 7, 8 table I, examples 2,4,7,8,9,13,14,15,16,17,18,22 see claims 1,10	1,12
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

30 October 1998

Date of mailing of the international search report

12/11/1998

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INTERNATIONAL SEARCH REPORT

Int .ional Application No

PCT/US 98/13419

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 26 35 876 A (E. I. DU PONT DE NEMOURS AND CO.) 3 March 1977 see page 3, line 1 - line 11 see page 35, examples 26,28,33,34,35,36 see claims 1,18 ---	1,12
X	DE 28 05 167 A (E. I. DU PONT DE NEMOURS AND CO.) 10 August 1978 see page 7, line 1 see page 26, line 30 - line 31 see page 30, line 15 see claims 1,14 ---	1,12
X	DE 28 05 166 A (E. I. DU PONT DE NEMOURS AND CO.) 10 August 1978 see page 9, line 1 see page 33, first compound see claims 1,16 ---	1,12
X	US 4 190 666 A (S. C. CHERKOFKY ET AL.) 26 February 1980 see table I, examples 26,28,33,34,35,36 see claims 1,29 ---	1,12
X	WO 88 01167 A (SMITHKLINE BEECHAM CORP.) 25 February 1988 see page 8, compound no. 1 see claim 1 ---	1,12
X	EP 0 004 648 A (CIBA-GEIGY AG) 17 October 1979 see example 1, first paragraph; example 4, third and sixth compound; example 5, compound "2-Propylthio-4(5)-phenyl-5(4)-(3-pyridyl)-imidazol" see page 5 ---	1,12
P,X	US 5 656 644 A (J. L. ADAMS ET AL.) 12 August 1997 see column 5, line 36 - line 49 see column 12, line 65 see column 13, line 16 - line 17 see column 14, line 66 - line 67 see claims 1,11 ---	1,12
X	WO 92 04330 A (SMITHKLINE & FRENCH LABORATORIES LTD.) 19 March 1992 see the starting compounds of the following examples: 1,4,6,7,20,28,29,32 ---	1
X	AT 374 198 B (CIBA-GEIGY AG) 26 March 1984 see starting compound of example 1 see page 11, line 9 see page 11, line 20 ---	1
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/13419

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 372 964 A (J. G. WHITNEY) 8 February 1983 see table 4, example 41 see claims 1,10 ---	1
X	EP 0 522 887 A (RHONE-POULENC RORER LTD.) 13 January 1993 see page 8, line 30 ---	1
Y	EP 0 043 788 A (SCHERING AG) 13 January 1982 see page 6, compound no. VI see claims 1,16 ---	1,12
Y	US 4 330 552 A (S. C. CHERKOFISKY) 18 May 1982 see claims 1,2; tables ---	1,12
Y	EP 0 032 113 A (E. I. DU PONT DE NEMOURS AND CO.) 15 July 1981 see claims 1,8; table 1 ---	1,12
X,Y	PATENT ABSTRACTS OF JAPAN vol. 11, no. 300 (C-449), 29 September 1987 & JP 62 093278 A (YOSHITOMI PHARMACEUT IND LTD), 28 April 1987 see abstract ---	1,12
Y	PATENT ABSTRACTS OF JAPAN vol. 12, no. 213 (C-505), 17 June 1988 & JP 63 010767 A (YOSHITOMI PHARMACEUT IND LTD), 18 January 1988 see abstract ---	1,12
Y	PATENT ABSTRACTS OF JAPAN vol. 13, no. 42 (C-564), 30 January 1989 & JP 63 239274 A (TOYAMA CHEM CO LTD), 5 October 1988 see abstract ---	1,12
A	J. P. WHITTEN ET AL.: JOURNAL OF ORGANIC CHEMISTRY, vol. 51, 1986, pages 1891-4, XP002082708 ---	1
A	B. H. LIPSHUTZ ET AL.: TETRAHEDRON LETTERS, vol. 27, no. 35, 1986, pages 4095-8, XP002082709 -----	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/13419

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15-19
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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